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## ORIGINAL ARTICLE

# Nasal high flow therapy and $\text{PtCO}_2$ in stable COPD: A randomized controlled cross-over trial

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## ABSTRACT

**Background and objective:** Hypercapnia is associated with worse clinical outcomes in exacerbations of COPD. The present study aimed to determine the effects of nasal high flow (NHF) therapy on transcutaneous partial pressure of carbon dioxide ( $\text{PtCO}_2$ ) in stable COPD patients.

**Methods:** In a single-blind randomized controlled cross-over trial, 48 participants with COPD were allocated in random order to all of four 20 min interventions: NHF at 15 L/min, 30 L/min and 45 L/min or breathing room air with each intervention followed by a washout period of 15 min. The primary outcome measure was  $\text{PtCO}_2$  at 20 min, adjusted for baseline  $\text{PtCO}_2$ . Secondary outcomes included respiratory rate at 20 min, adjusted for baseline. **Results:** The mean (95% CI) change in  $\text{PtCO}_2$  at 20 min was  $-0.6$  mm Hg ( $-1.1$  to  $0.0$ ),  $P = 0.06$ ;  $-1.3$  mm Hg ( $-1.9$  to  $0.8$ ),  $P < 0.001$ ; and  $-2.4$  mm Hg ( $-2.9$  to  $-1.8$ ),  $P < 0.001$ ; for NHF at 15 L/min, 30 L/min and 45 L/min compared with room air, respectively. The mean (95% CI) change in respiratory rate at 20 min was  $-1.5$  ( $-2.7$  to  $-0.3$ ),  $P = 0.02$ ;  $-4.1$  ( $-5.3$  to  $-2.9$ ),  $P < 0.001$ ; and  $-4.3$  ( $-5.5$  to  $-3.1$ ),  $P < 0.001$ ; breaths per minute compared with room air, respectively.

**Conclusion:** NHF results in a small flow-dependent reduction in  $\text{PtCO}_2$  and respiratory rate in patients with stable COPD.

**Clinical trial registration:** ACTRN12615000471583 at anzctr.org.au

**Key words:** arterial partial pressure, carbon dioxide, chronic obstructive respiratory disease, nasal high flow, randomized controlled trial.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; NHF, nasal high flow; NIV, non-invasive ventilation; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide;  $\text{PtCO}_2$ , transcutaneous partial pressure of carbon dioxide; RIP, Respiratory Inductance Plethysmography; StO<sub>2</sub>, transcutaneous oxygen saturation.

## SUMMARY AT A GLANCE

In patients with stable COPD, the administration of nasal high flow results in flow-dependent reductions in transcutaneous partial pressure of carbon dioxide and respiratory rate.

## INTRODUCTION

In acute exacerbations of COPD, hypercapnia is associated with worse clinical outcomes including death.<sup>1</sup> Non-invasive ventilation (NIV) is recommended to provide respiratory support to patients with exacerbations of COPD who have hypercapnic respiratory failure despite optimal medical therapy.<sup>2</sup> Tolerability of NIV may be a barrier to effective use<sup>3</sup> and an alternative to NIV is a priority for the management of acute exacerbations of COPD.

Nasal high flow (NHF) therapy may cause a modest reduction in the partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) in both stable and acute COPD.<sup>4–9</sup> However, the interpretation of studies of NHF, and their applicability to clinical practice, remains variably limited by the confounding effect of concomitant oxygen therapy, absence of randomized controlled treatments and a lack of data on the dose–response relationship across the range of flows used in clinical practice.

The present study is a randomized controlled cross-over trial of the effect of three different flow rates of NHF therapy compared with a control intervention of room air, in patients with stable COPD who do not need concomitant oxygen therapy. The main objective of the present study was to determine the flow–response relationship of NHF therapy and PaCO<sub>2</sub> in stable COPD. The hypothesis was that NHF therapy would cause a flow-dependent reduction in PaCO<sub>2</sub> and respiratory rate in stable COPD.

## METHODS

In this single-blind, randomized, controlled, four-way cross-over trial, 48 participants with a doctor's diagnosis of COPD, aged at least 40 years and with a tobacco

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smoking history of  $\geq 10$  pack years were recruited. Participants were excluded if their forced expiratory volume in 1 s ( $FEV_1$ )/ forced vital capacity ratio was  $>0.7$ , or if they were on long-term oxygen therapy, had a current exacerbation of COPD requiring a short course of antibiotics or oral glucocorticoids or oxygen therapy, or hospitalization for an acute exacerbation of COPD within the last 6 weeks. People with nasal conditions potentially affecting the ability to use NHF were also excluded. Eligible participants attended a single study visit at the MRINZ Respiratory Physiology Laboratory at Wellington Regional Hospital.

The present study was prospectively registered with ANZCTR (Trial ID: ACTRN12615000471583) and approved by the Health and Disability Ethics Committee of New Zealand (Ref: 15/NTA/4). Full written informed consent was completed before any study-specific procedures.

After demographic data was collected, spirometry was performed in accordance with American Thoracic Society/European Respiratory Society criteria<sup>10</sup> using a Jaeger Master screen body volume constant plethysmography unit with pneumotachograph and diffusion unit (Erich-Jaeger, Wurzburg, Germany). Measurements of transcutaneous partial pressure of carbon dioxide ( $PtCO_2$ ), transcutaneous oxygen saturation ( $StO_2$ ) and heart rate were made using the SenTec transcutaneous monitor (SenTec digital monitor with V-Sign Sensor VS-A/P/N, Therwil, Switzerland; further details in the Appendix S1 in Supplementary Information). The SenTec probe was kept on the patient for between 20 and 30 min before the subsequent study procedures to ensure a stable baseline measurement of  $PtCO_2$ .

Minute ventilation was measured using Respiratory Inductance Plethysmography (RIP) bands (QDC-Pro device; CareFusion, Yorba Linda, California, USA). Further details are given in the Appendix S1 in Supplementary Information.

Participants received all interventions for 20 min in a randomized order while seated. Each NHF flow setting was at a temperature of  $37^\circ\text{C}$  without oxygen: 15 L/min, 30 L/min or 45 L/min; or the control setting of breathing room air only without the NHF attached, using the myAIRVO 2 device (PT101AZ; Fisher and Paykel Healthcare, Auckland, New Zealand). Further details are given in the Appendix S1 in Supplementary Information.

Each of the four interventions was followed by a washout period breathing room air for at least 15 min, allowing the  $PtCO_2$  to return to within 4 mm Hg of the baseline measurement for the particular intervention. The washout could be extended until this criterion was met.

$PtCO_2$ ,  $StO_2$ , heart rate and respiratory rate were recorded at the start of each intervention and then every 5 min until the end of each washout period.

The order of administration of the four treatments was randomized. The randomisation was computer-generated by the study statistician, who had no role in the recruitment, study visits or data collection. Treatment allocation and maintenance of blinding are described in the Appendix S1 in Supplementary Information.

Participant tolerability questionnaires were administered during the washout periods after each NHF intervention. Participants rated the ease of application, level of comfort, weight of the nasal interface, noisiness, amount of moisture in the nasal passages and likelihood of reusing the system on a continuous scale from most positive (0) to least positive (100).

## Outcomes

The primary outcome was  $PtCO_2$  at 20 min, adjusted for baseline  $PtCO_2$ . Secondary outcomes were: the proportion of participants who had a decrease in  $PtCO_2 \geq 4$  mm Hg from baseline during the intervention;  $PtCO_2$ , respiratory rate,  $StO_2$ , heart rate and minute ventilation adjusted for baseline for each 5-min time-point during the intervention and the subsequent 15 min washout period; the proportion of participants who withdrew from the intervention before it was completed; and results of the tolerability questionnaires.

## Statistical analysis

The paired SDs of  $PtCO_2$  in a previous study investigating oxygen administration to patients with stable COPD were between 1.8 and 4.4 mm Hg.<sup>11</sup> Based on the highest  $PtCO_2$  SD of 4.4 mm Hg, and an alpha value of 0.0083 (to take into account the potential for six possible comparisons for the four-way cross-over study) a sample size of 48 had 90% power to detect a difference in  $PtCO_2$  of 3.8 mm Hg.

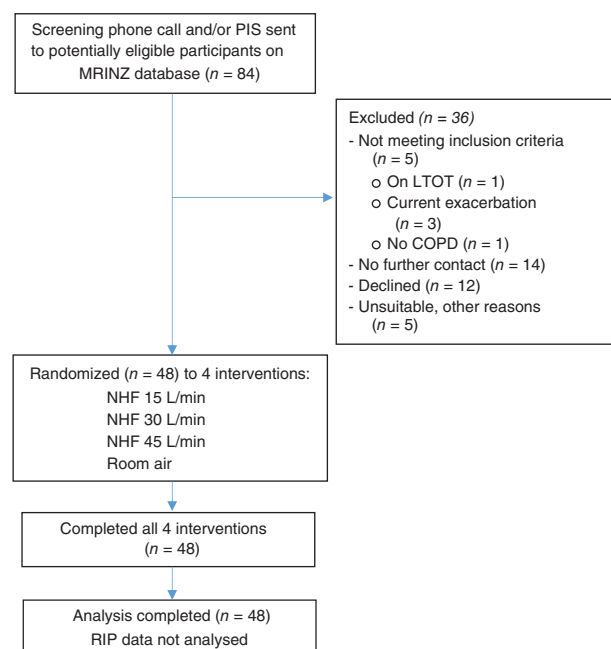
The comparison of each of the three NHF treatments compared to room air was by mixed linear model with fixed effects for the randomisation sequence, the baseline measurement of the particular variable, and the randomized treatment, time and their interaction; and a random effect for each participant, with an exponential time correlation structure for the repeated measurements. The comparison of paired proportions for those that had a decrease from baseline  $PtCO_2$  of  $\geq 4$  mm Hg was by an exact McNemar's test and estimation of the CI for the differences in paired proportions, NHF intervention minus room air, by an asymptotic method. The comparison of device questionnaire scores was by a mixed linear model with fixed effects for the randomization sequence and treatment; and a random effect for the participant. In a post hoc analysis, the statistical test of whether the  $PtCO_2$  response to treatment differed by whether the baseline  $PtCO_2$  was  $>45$  mm Hg or not was the interaction  $P$  value. The above-mentioned analysis was carried out using the SAS (SAS, Cary, NC, USA) version 9.4 package.

## RESULTS

### Participant characteristics

Contact was made with 84 potentially eligible participants of whom 48 were randomized between May 2015 and February 2016 (Fig. 1).

Three participants required an extended washout in at least one of the interventions past the planned 15 min washout for the  $PtCO_2$  to return to within 4 mm



**Figure 1** Participant flow through the study and allocation of interventions. LTOT, long-term oxygen therapy; NHF, nasal high flow; PIS, participant information sheet; RIP, Respiratory Inductance Plethysmography.

Hg of the time point zero reading, with the longest extension being 10 min.

Participant characteristics are shown in Table 1. Twenty-nine of the participants were male and 6/48 (12.5%) were hypercapnic, with  $\text{PtCO}_2 > 45$  mm Hg, at randomization. Twenty-four participants (50%) had severe or very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.<sup>12</sup>

### Transcutaneous partial pressure of carbon dioxide

The mean  $\text{PtCO}_2$  adjusted for baseline after 20 min compared to room air was lower for NHF with a flow-dependent reduction in  $\text{PtCO}_2$  (Table 2). The mean difference in  $\text{PtCO}_2$  compared to room air was  $-2.4$  mm Hg (95% CI:  $-2.9$  to  $-1.8$ ),  $P < 0.001$ ,  $-1.3$  mm Hg (95% CI:  $-1.9$  to  $-0.8$ ),  $P < 0.001$  and  $-0.6$  mm Hg (95% CI:  $-1.1$  to  $0.0$ ),  $P = 0.06$  for NHF at 45 L/min, 30 L/min and 15 L/min, respectively. There was no significant interaction between treatment response and whether the baseline  $\text{PtCO}_2$  was greater than 45 mm Hg or not,  $P = 0.74$ .

The proportion of participants with at least one measurement of  $\text{PtCO}_2$  which decreased from baseline  $\geq 4$  mm Hg, up to and including the 20-min treatment period was 15/48 (31.2%), 8/48 (16.7%) and 2/48 (4.2%) for NHF at 45 L/min, 30 L/min and 15 L/min, respectively, and 1/48 (2.1%) for room air. The paired proportions difference for NHF minus room air was 29.7% (95% CI: 16.3–42.0),  $P < 0.001$ , 14.6% (95% CI: 4.6–24.6),  $P = 0.016$  and 2.1% (95% CI:  $-2.0$  to 6.1),  $P = 0.99$ , for NHF at 45 L/min, 30 L/min and 15 L/min, respectively. Four participants (8.3%) had at least one

measurement of  $\text{PtCO}_2$  which decreased from baseline  $\geq 8$  mm Hg, up to and including the 20-min treatment period for NHF at 45 L/min.

### Respiratory rate

There were significant reductions in respiratory rate between NHF compared to room air at 20 min with a flow rate dependent effect (Table 3). The maximum point estimate difference in respiratory rate was  $-5.0$  breaths per minute (95% CI:  $-6.2$  to  $-3.8$ ),  $P < 0.001$ , at 5 min with NHF at 45 L/min compared to room air, representing a 28% reduction from the baseline respiratory rate.

### Oxygen saturation and heart rate

The  $\text{StO}_2$  was higher for NHF 45 L/min compared to room air at the 5, 15 and 20 min time points. The mean maximum difference in  $\text{StO}_2$  was 0.8% (95% CI: 0.41–1.28),  $P < 0.001$ , observed after 5 min for NHF 45 L/min compared to room air (Table S1 (Supplementary Information)).

Heart rate remained largely constant throughout the interventions with no statistically significant differences between any of the NHF interventions and room air, with the exception of the 20-min time point for the 15 L/min where it was 2 beats per minute higher (95% CI: 0.25–3.8),  $P = 0.025$  (Table S2 (Supplementary Information)).

The full-set of mean data for each variable is shown in the Tables S3–S6 in Supplementary Information.

### Minute ventilation

In 97/192 (51%) interventions, the RIP measurements were valid, and of the 144 planned comparisons between NHF and room air, in only 52 (36%) were both NHF and room air measurements valid. For this reason, the RIP data is not presented.

### Tolerability questionnaires

Participant feedback was that NHF at 45 L/min was less comfortable and noisier, but moister than NHF at 15 L/min (Table 4). NHF at 30 L/min was generally more tolerable than 45 L/min.

## DISCUSSION

The NHF device resulted in a small flow-dependent reduction in the  $\text{PtCO}_2$  in participants with stable COPD. There was a marked flow-dependent reduction in respiratory rate with the use of NHF. These findings suggest a favourable physiological effect with NHF in stable COPD.

There are a number of methodological issues relevant to the interpretation of the study findings. Our study was single-blinded in that although participants were blinded to the actual flow rate they received, they could feel the difference between low, medium and high flows. The interventions were applied for 20 min periods, which was sufficient time to observe an effect on  $\text{PtCO}_2$  with the maximum change usually observed at the 5-min time point. There was a washout period

**Table 1** Baseline participant characteristics

Characteristic <i>n</i> = 48 for all	Mean (SD)	Median (IQR)	Min to max
Age (years)	69.4 (8.6)	70 (62–74)	52–87
BMI (kg/m <sup>2</sup> )	27.6 (6.7)	25.7 (53.4–30.3)	14.5–48.4
FEV <sub>1</sub> (L)	1.55 (0.64)	1.44 (1.03–1.87)	0.50–3.0
FEV <sub>1</sub> /FVC (%)	47.2 (11.5)	47.5 (36.2–55.1)	28.4–66.9
FEV <sub>1</sub> % predicted	52.5 (19.6)	49.6 (37.2–68.2)	18.5–88.6
FVC (L)	3.24 (0.88)	3.10 (2.58–3.90)	1.63–5.41
Smoking pack years	46.1 (31.2)	41.5 (30.0–58.0)	13.0–200.0
MMRC	1.17 (0.31)	1 (0–2)	0–3
PtCO <sub>2</sub> (mm Hg)	37.8 (6.1)	36.7 (33.8–39.6)	28.8–55.8
StO <sub>2</sub> (%)	94.9 (2.4)	95.0 (94.1–97.0)	88–99
Respiratory rate (breaths per minute)	17.8 (5.5)	16.5 (14.0–21.5)	7.0–30.0
Heart rate (beats per minute)	74.6 (14.1)	74.5 (66.6–81.0)	48.0–118
<i>n</i> /48 (%)			
Gender male			29 (60.4)
<i>Co-morbidities</i>			
Asthma			4 (8.3)
Bronchiectasis			1 (2.1)
Heart failure			3 (6.3)
<i>Ethnicity</i>			
European			32 (66.7)
Maori			9 (18.8)
Other			6 (12.5)
Pacific			1 (2.1)
<i>Treatment</i>			
Inhaled corticosteroid			34 (70.8)
Long-acting beta-agonist			34 (70.8)
Long-acting muscarinic antagonist			19 (40.0)
Short-acting beta-agonist			34 (70.8)
Short-acting muscarinic antagonist			15 (31.3)

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; MMRC, Modified Medical Research Council; PtCO<sub>2</sub>, transcutaneous carbon dioxide, StO<sub>2</sub>, transcutaneous oxygen saturation.

which allowed each of the four intervention periods to begin within a similar baseline PtCO<sub>2</sub>.

The external validity of the findings was limited in the respect that participants with stable COPD were recruited, rather than during a severe exacerbation, in which NHF is more likely to be administered. However, this design enhanced the internal validity, allowing a cross-over design to be utilized with a single study visit, which importantly enabled a stable baseline PtCO<sub>2</sub> to be achieved before each intervention. It also avoided the confounding effect of supplemental oxygen use, a potential limiting factor in previous studies of NHF therapy in exacerbations of COPD, in which lower inspired concentrations of oxygen with NHF may have contributed to the reductions in PaCO<sub>2</sub> observed.<sup>4–6</sup> There was a broad cross-section of severity of COPD, with one in eight having hypercapnia and one in two having an FEV<sub>1</sub> < 50% predicted. A post hoc analysis showed no evidence that the change in PtCO<sub>2</sub> in response to treatment varied by whether the patient was in chronic hypercapnic respiratory failure.

The transcutaneous SenTec monitor has been validated and used as a surrogate measure of PaCO<sub>2</sub>, allowing continuous monitoring and the avoidance of multiple arterial blood gas punctures.<sup>13–17</sup> The RIP

measures were not valid for most interventions and so it was not possible to directly measure the effect of NHF on minute ventilation or tidal volume.

Our observations showed that NHF reduces PtCO<sub>2</sub> in a flow-dependent manner complements previous work. The small reduction in PtCO<sub>2</sub> of 2.4 mm Hg at 45 L/min is similar to the 3.4 mm Hg reduction with NHF at 30 L/min for 20 min in COPD patients on long-term oxygen therapy,<sup>4</sup> the 3.1 mm Hg reduction with NHF at 20 L/min for 45 min in COPD patients requiring supplemental oxygen at 2 L/min in hospital,<sup>6</sup> and the reduction of 1.4 mm Hg observed in our previous study of patients hospitalized with exacerbations of COPD, where supplemental oxygen delivered with NHF was titrated to maintain patient StO<sub>2</sub> at hospital pre-study levels.<sup>7</sup> However, it is less than the 5.2 mm Hg and 7.3 mm Hg reduction in PtCO<sub>2</sub> observed with 2 h of NHF treatment, at 20 L/min and 30 L/min respectively, in the uncontrolled trial of hospitalized COPD patients<sup>8</sup> and the non-significant 4.0 mm Hg and 5.5 mm Hg reduction in PaCO<sub>2</sub> in COPD patients with chronic hypercapnic respiratory failure receiving NHF therapy for 30 min at 20 L/min and 30 L/min, respectively.<sup>9</sup> While the mean reduction in PtCO<sub>2</sub> of 2.4 mm Hg found in our study is of uncertain clinical

**Table 2**  $\text{PtCO}_2$  values and mixed linear models for difference in  $\text{PtCO}_2$  of NHF minus room air adjusted for baseline (time zero)

Time point (min)	NHF 15 L/min			NHF 30 L/min			NHF 45 L/min		
	Air	NHF–air difference from baseline (mm Hg)		NHF–air difference from baseline (mm Hg)		NHF–air difference from baseline (mm Hg)		NHF–air difference from baseline (mm Hg)	
	$\text{PtCO}_2$ (mm Hg) Mean (SD)	$\text{PtCO}_2$ (mm Hg) Mean (SD)	P value	$\text{PtCO}_2$ (mm Hg) Mean (SD)	$\text{PtCO}_2$ (mm Hg) Mean (SD)	P value	$\text{PtCO}_2$ (mm Hg) Mean (SD)	$\text{PtCO}_2$ (mm Hg) Mean (SD)	P value
0	38.4 (5.5)	37.9 (5.5)	–0.95 (–1.53 to –0.37) $P = 0.001$	38.0 (5.6)	38.2 (5.1)	–1.43 (–2.00 to –0.85) $P < 0.001$	36.3 (6.0)	38.2 (5.1)	–2.21 (–2.78 to –1.63) $P < 0.001$
5	38.6 (5.3)	37.4 (5.3)		37.0 (5.9)	36.3 (6.0)		36.3 (6.0)	36.3 (6.0)	
10	38.6 (5.3)	37.6 (5.4)	–0.74 (–1.31 to –0.16) $P = 0.012$	36.9 (6.1)	36.0 (6.1)	–1.51 (–2.09 to –0.94) $P < 0.001$	36.0 (6.1)	36.0 (6.1)	–2.47 (–3.05 to –1.90) $P < 0.001$
15	38.7 (5.2)	37.9 (5.3)	–0.50 (–1.08 to 0.07) $P = 0.087$	37.1 (6.0)	36.4 (5.9)	–1.44 (–2.01 to –0.86) $P < 0.001$	36.4 (5.9)	36.4 (5.9)	–2.15 (–2.72 to –1.57) $P < 0.001$
20	38.8 (5.0)	38.0 (5.3)	–0.55 (–1.12 to 0.03) $P = 0.063$	37.3 (6.0)	36.3 (5.6)	–1.32 (–1.90 to –0.75) $P < 0.001$	36.3 (5.6)	36.3 (5.6)	–2.37 (–2.94 to –1.79) $P < 0.001$

NHF, nasal high flow;  $\text{PtCO}_2$ ; transcutaneous partial pressure of carbon dioxide.**Table 3** Mixed linear models for difference in respiratory rate of NHF minus room air adjusted for baseline (time zero)

Time points (min)	NHF 15 L/min			NHF 30 L/min			NHF 45 L/min		
	Air	NHF–air difference from baseline (%) Mean (95% CI) P value		NHF–air difference from baseline (%) Mean (95% CI) P value		NHF–air difference from baseline (%) Mean (95% CI) P value		NHF–air difference from baseline (%) Mean (95% CI) P value	
	RR (bpm) Mean (SD)	RR (bpm) Mean (SD)		RR (bpm) Mean (SD)	RR (bpm) Mean (SD)		RR (bpm) Mean (SD)	RR (bpm) Mean (SD)	
0	18.2 (4.7)	17.6 (4.9)	–2.45 (–3.65 to –1.24) $P < 0.001$	18.1 (5.7)	18.3 (4.8)	–4.59 (–5.79 to –3.39) $P < 0.001$	12.9 (5.5)	18.3 (4.8)	–4.98 (–6.19 to –3.78) $P < 0.001$
5	17.9 (4.9)	15.4 (4.9)		13.3 (4.8)	12.9 (5.5)		12.9 (5.5)	12.9 (5.5)	
10	17.1 (4.6)	15.0 (5.0)	–1.99 (–3.19 to –0.78) $P = 0.001$	12.6 (4.4)	12.9 (5.7)	–4.42 (–5.63 to –3.22) $P < 0.001$	12.9 (5.7)	12.9 (5.7)	–4.13 (–5.33 to –2.93) $P < 0.001$
15	17.1 (4.9)	15.9 (5.3)	–1.15 (–2.36 to 0.05) $P = 0.061$	13.6 (5.2)	12.9 (5.0)	–3.53 (–4.73 to –2.32) $P < 0.001$	12.9 (5.0)	12.9 (5.0)	–4.23 (–5.44 to –3.03) $P < 0.001$
20	17.5 (4.8)	16.0 (5.7)	–1.47 (–2.67 to –0.26) $P = 0.017$	13.4 (5.2)	13.3 (4.8)	–4.13 (–5.34 to –2.93) $P < 0.001$	13.3 (4.8)	13.3 (4.8)	–4.25 (–5.46 to –3.05) $P < 0.001$

bpm: breaths per minute; NHF, nasal high flow; RR, respiratory rate

**Table 4** Mixed linear models for difference in questionnaire responses between NHF interventions. Values are on a continuous scale from most positive (0) to least positive (100)

Question	Mean difference (95% CI)		P overall
	P value for individual comparison		
	NHF 30 L/min minus NHF 15 L/min	NHF 45 L/min minus NHF 15 L/min	
Ease of application	3.7 (0.7 to 6.7) P = 0.017	2.7 (−0.3 to 5.8) P = 0.076	0.046
Overall comfort	11.0 (4.5 to 17.4) P = 0.001	20.2 (13.8 to 26.7) P < 0.001 <sup>†</sup>	<0.001
Moisture in nasal passages	−0.02 (−4.3 to 4.2) P = 0.99	−7.7 (−11.9 to −3.4) P < 0.001	<0.001
Noisiness	11.6 (4.1 to 19.1) P = 0.003	28.4 (20.9 to 35.9) P < 0.001	<0.001
Likelihood of reusing NHF	3.0 (−2.9 to 9.0) P = 0.31	2.5 (−3.4 to 8.5) P = 0.40	0.55
Weight of nasal cannula	1.5 (−3.5 to 6.4) P = 0.56	3.1 (−1.8 to 8.1) P = 0.21	0.46

NHF, nasal high flow.

<sup>†</sup>n = 47.

significance, the reduction in  $\text{PtCO}_2$  from baseline of  $\geq 8$  mm Hg in 4/48 participants on NHF at 45 L/min suggests this therapy may have clinically important effects on  $\text{PtCO}_2$  in a proportion of patients with COPD.

The reduction in respiratory rate with NHF we observed has been reported in healthy volunteers,<sup>18</sup> in COPD patients,<sup>4–6,19</sup> and in other clinical situations such as pulmonary fibrosis and post-cardiac surgical patients.<sup>5,20</sup> The magnitude of the reduction in respiratory rate was marked with a maximum 5 breaths per minute reduction after 5 min of NHF at 45 L/min, representing a >25% reduction in respiratory rate. It has recently been reported that in patients with COPD and chronic hypercapnic respiratory failure that a reduction in respiratory rate of this magnitude with NHF therapy is associated with reduced respiratory muscle load, with a reduction in transdiaphragmatic pressures and an increase in expiratory time.<sup>9</sup>

The flow-dependent physiological effects on  $\text{PtCO}_2$  and respiratory rate we observed with NHF in COPD patients was consistent with the observed flow-dependent increase in airway pressure, end expiratory pressures, end expiratory lung volume and inspiratory pressures observed in post-cardiac surgery patients,<sup>20,21</sup> and airway pressures in healthy volunteers<sup>18</sup> and COPD patients.<sup>8</sup> The modest reduction in  $\text{PtCO}_2$  indicates alveolar ventilation was increased despite the marked reduction in respiratory rate. The relative contributions of increases in alveolar volume and/or reductions in physiological dead space to the increase in alveolar ventilation were not assessed in this study. Other mechanisms which may play a role but were not assessed in the study include an increase in tidal volume, a small positive end-expiratory pressure effect, reduction in upper airway resistance and improved mucociliary clearance from humidification of the airways.<sup>4,8,22–24</sup>

Previous studies have shown improved tolerability of NHF compared to both face masks and standard nasal

prongs<sup>25–27</sup> and it was generally well tolerated in our study. Given NHF at 30 L/min reduced  $\text{PtCO}_2$  and respiratory rate by a similar amount to NHF at 45 L/min, but was more comfortable, this flow rate may be preferred in clinical practice.

In conclusion, NHF results in a small reduction in  $\text{PtCO}_2$  and a marked reduction in respiratory rate, in a flow-dependent manner with the higher the flow the greater the effect. Further studies need to be undertaken to compare NHF against the gold standard of NIV in acute exacerbations of COPD associated with respiratory failure.

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## Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

## Appendix S1 Methods.

**Table S1** Mixed linear models for Oxygen saturation difference in NHF minus room air adjusted for baseline (time zero).

**Table S2** Mixed linear models for Heart rate difference in NHF minus room air adjusted for baseline (time zero).

**Table S3** Data description for transcutaneous carbon dioxide (PtCO<sub>2</sub>) by intervention and time.

**Table S4** Data description for respiratory rate by intervention and time.

**Table S5** Data description for heart rate by intervention and time.

**Table S6** Data description for transcutaneous oxygen saturation (StO<sub>2</sub>) by intervention and time.